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(57) Abstract

A preparation for pharmaceutical use, especially in the treatment of migraine, cluster headaches, arthritis and bronchial complaints, comprises a sesquiterpene lactone such as parthenolide and B-complex vitamins such as riboflavin (vitamin B_2), as well as a method of treating and providing prophylaxis against such illnesses by use of such a combination.

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COMBINATIONAL DRUGS FOR TREATING MIGRAINE AND OTHER ILLNESSES, COMPRISING SESQUITERPENE LACTONES AND B-COMPLEX VITAMINS

FIELD OF THE INVENTION

This invention relates to compositions and methods useful in the treatment of migraine headaches and related illnesses.

BACKGROUND OF THE INVENTION

The incidence of migraine including cluster headaches, is said to be approximately 10-20% of the male population and 20-30% of the female population. Treatment for many patients having the occasional migraine involves simple analgesics with or without sedatives. Approximately 10% of migraine sufferers have three or more attacks per month and warrant prophylactic treatment. Twenty-five to fifty percent of this group benefit from treatment with beta-adrenoreceptor blocking agents, clonidine or, in the female sufferer, gestagen hormones. In the remaining population of migraine sufferers, and in those with intolerable side-effects from available drugs, there is a lack of conventional pharmaceutical preparations that exhibit therapeutic effect, without severe side-effects.

Feverfew, rich in sesquiterpene lactones, principally parthenolide, has also been shown to have a prophylactic effect against migraine. In one study, more than 70% of the feverfew users claimed that the herb had decreased the frequency of their attacks, caused them to be less painful, or both. In another study, sixty-eight percent of migraine sufferers displayed improvement when treated prophylactically with riboflavin.

Although the precise cause or causes of migraine, arthritis, and asthma remain unknown, all three diseases are associated with a postulated local or systemic release of active substances including, in the case of migraine and/or its variants: norepinephrine (noradrenaline), 5-hydroxytryptamine (serotonin), histamine, prostaglandins and bradykinin; in the case of arthritis; prostaglandins,

histamine, 5-hydroxytryptamine and bradykinin; and in the case of asthma; histamine, 5-hydroxytryptamine, bradykinin, acetylcholine, prostaglandins and the leukotrienes. These endogenous substances have in common the ability to cause smooth muscle to contract (i.e. go into spasm), and many are also pain-producing substances, e.g. 5-hydroxytryptamine, bradykinin, histamine and prostaglandins. Non-selective antagonist drugs will, therefore, not only reduce the smooth muscular spasm (of intracranial blood vessels in the case of migraine, or bronchial smooth muscle in the case of asthma) but also the pain (of migraine and arthritis) associated with their release.

Sesquiterpene lactones are known to be present in many plants, for example in *Asteracea*, *Magnoliaceae*, and in particular in *Tanacetum parthenium* (feverfew), and are thought to be responsible for observed bioactivity of the leaf material.

SUMMARY OF THE INVENTION

It has now been discovered that a mixture of a sesquiterpene lactone and a B-vitamin, is especially effective in both the treatment and prophylaxis of migraine, arthritis, and asthma.

In accordance with the present invention, a sesquiterpene lactone, or a source of sesquiterpene lactones, such as sesquiterpene lactone-containing plants and plant extracts, is used in combination with a B-complex vitamin, such as riboflavin. Preparations comprising such a combination are also provided that have pharmaceutical use, particularly in the treatment of migraine, including cluster, headaches and various arthritic and bronchial conditions, such as asthma.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The B-complex vitamin that is useful in accordance with the present invention includes riboflavin, riboflavin phosphate, flavin adenine dinucleotide, nicotinic acid, folic acid, cyanocobalmin, para-amino benzoic acid, thiamine,

pyridoxine, pantothenic acid, biotin, choline inositol, and carnitine.

The sesquiterpene lactone that is useful in accordance with the present invention includes germacranolides, guaianolides, and pseudoguaianolides, in particular those sesquiterpene lactones having an α-methylene substituent in the lactone ring, such as parthenolide. Parthenolide and sesquiterpene lactone-containing plant materials, such as feverfew leaf or extracts from such plant materials are preferred. These natural-sources of actives are preferred because they deliver many active components, not only a single chemical entity. The variety of active components and active chemical species present results in preparations with a broader spectrum of activity compared to pure sesquterpine lactones.

Although both sesquiterpene lactones and B-complex vitamins have been found, individually, to be effective for treatment or prophylaxis of migraine, the combination of the two types of actives, in accordance with the present invention, leads to synergistic effects. Thus, a combination of feverfew or other source of parthenolide with a B-vitamin additive leads to a further decrease in the frequency of the attacks and causes the attacks to be less painful. An increased percentage of migraine sufferers should therefore display an improvement in frequency, severity, or both, when treated prophylactically with the combinational drug. The combinational drug has low toxicity, surprisingly few side-effects and may be taken for the extended periods required for effective prophylaxis, without adverse reactions.

Dosage And Pharmaceutical Preparation

The dosage of active ingredients will, of course, vary from individual to individual and will depend upon many factors, including body weight, metabolism, and the like. In general, however, it is believed that, in both treatment and prophylaxis, a given individual should receive from about 50 to about 10,000 micrograms, preferably from about 250 to about 1000 micrograms, and most preferably about 250 micrograms of sesquiterpene lactone, such as

parthenolide, per day. In general, it is also believed that a given individual should receive from about 0.1 to about 5,000 milligrams, preferably from about 100 to about 500 milligrams, and most preferably about 400 milligrams of B-complex vitamin, especially riboflavin, per day. More, however, may be need in the case of acute attacks.

Thus, in accordance with the present invention, pharmaceutical dosage forms are provided that contain from about 50 to about 10,000 micrograms, preferably from about 250 to about 1000 micrograms, and most preferably about 250 micrograms of sesquiterpene lactone, such as parthenolide, in combination with about 0.1 to about 5,000 milligrams, preferably from about 100 to about 500 milligrams, and most preferably about 400 milligrams of B-complex vitamin, especially riboflavin, per day.

In general, such pharmaceutical dosage forms may comprise from about 5 to 300 mg, especially 50 to 200 mg, of feverfew leaf, containing about 250 micrograms of parthenolide, in combination with from about 0.1 to 400 mg of riboflavin per day. For treatment, more than one dose may be required, as in the case of the treatment of an acute attack of migraine or allied disorder. The feverfew dosage may be adjusted to accommodate the naturally variable levels of sesquiterpene lactones, such as parthenolide. A particularly preferred capsule contains about 125 mg of high-parthenolide feverfew and 400 mg of riboflavin. It is preferred that the composition of the present invention be administered as two tablets daily; each tablet containing 125 mg feverfew (containing 250 mg of sesquiterpene lactone) and 200 mg riboflavin or other B-complex vitamin. The combination of actives may also be administered by independent dosage forms. For example, two tablets of feverfew, each containing 250 µgrams of parthenolide may be taken daily in addition to two tablets of B complex vitamin, each containing 200 mgrams of riboflavin.

For the treatment or prophylaxis of migraine the preparations may be administered orally, or parenterally and conveniently take the form of a tablet, caplet, capsule, lozenge, injectable solution, liquid suspension or elixir.

Circumstances may arise wherein the dose is best administered by suppository, inhalation, slow release implant, slow release patch or other topical vehicle.

The combination of active ingredients are usually best given in an oral form made up as a tablet, caplet, capsule, or as a liquid suspension or elixir one or two times daily. For oral administration, the preparation may be admixed with any conventional tableting or capsuling carrier, or as a suspension or solution in any orally acceptable non-toxic liquid carrier. If desired, the drug may be provided in encapsulated form for sustained release over a period of time. For parenteral administration the drug may be provided as a suspension or solution in any suitable, sterile injection medium, e.g. sterile aqueous saline solution. Given the desired dosage rates indicated above, the appropriate method of formulation of the drug in a form suitable for oral or parenteral administration will be obvious to persons skilled in the art. The same applies for inhalants and rectal or slow-release implant modes of administration, which are also feasible.

The pharmaceutical formulations may additionally include, in addition to the aforementioned active agents, other known anti-migraine preparations, sedatives and relaxants, analgesics and antiemetics such as:

Propranolol Hydrochloride
Ergotamine tartrate
Methysergide Maleate
Dihydroergotamine Mesylate
Clonidine Hydrochloride
Isometheptene Mucate
Buclizine Dihydrochloride
Metoclopramide Hydrochloride
Pizotifen Hydrogen Malate
Aspirin and other non-steroidal anti-inflammatory agents
White willow bark and its extracts
Other non-steroidal anti-inflammatory agents of plant origin

Paracetamol and other minor analgesics
Pentazocine Hydrochloride
Prochlorperazine
Caffeine
Meprobamate
Ethoheptazine Citrate
Zomepirac
Meptazinol Hydrochloride
DEH
Sumatriptin
Ginger
Brazilian Cocoa
Capsaicin
Magnesium
Melatonin
Vitamin D
Calcium
Chamomile
Milk Thistle
Valerian
Peppermint
Eucalyptus

Excellent efficacy of a preparation in accordance with this invention is likely in all forms of migraine including the treatment of classical and common migraine, migrainous neuralgia (cluster headache), and premenstrual and menstrual migraine and other headaches.

The compositions of the present invention may be used in the prevention of the aforementioned types of headache by reducing the frequency, severity and duration of the attacks and by reducing the nausea and vomiting symptoms.

The compositions may also be used to treat acute attacks of the aforementioned types of headache, by reducing their duration, severity and the intensity of associated symptoms.

For the treatment of arthritic conditions, preparations in accordance with the invention may be administered orally, or parenterally and conveniently take the form of a tablet, capsule, injectable, liquid suspension or elixir. Circumstances may arise where it is best administered by suppository, inhalation, slow release implant, slow release patch, or other topical vehicle. Dosage and administration are as indicated above.

A preparation in accordance with the invention may additionally include other anti-arthritis agents including non-steroidal anti-inflammatory drugs, analgesics, skeletal muscle relaxants, steroids, gold and penicillamine.

Examples of such agents are:

aspirin,
indomethacin,
piroxicam,
benorylate,
ibuprofen,
paracetamol,
salicylamine,
diflunizal,
ethoheptazine,
fenoprofen (calcium fenoprofate)
flufenamic acid,
mefenamic acid,
naproxen sodium,
ketoprofen,
phenylbutazone,
sulindac,

penicillamine,
salicylate,
fenclofenac,
flurbiprofen,
fenbufen,
feprazone,
sodium aurothiomalate,
naproxen,
benoxaprofen,
aloxipria,
hydroxychloroquine sulphate,
azapropazone,
tolemtin,
choline magnesium trisalicylate,
diclofenac,
adrenal steroids such as prednisone or prednisolone,
white willowbark and its extracts,
other non-steroidal anti-inflammatory agents of plant origin
evening primrose oil
gamma linoleic acid
borage oil
flax seed

The compositions of the present invention may be used in the treatment of rheumatoid arthritis, osteoarthritis, arthritis associated with Felty's syndrome, Still's disease, systemic lupus erythematosus, polyarteritis nodosa, scleroderma, gout, achalasia of the cardia, Crohn's disease, chronic brucellosis, ankylosing spondylitis, sarcoidosis, psoriasis and gonorrhoea.

The preparations are believed to be useful in the prevention of the above arthritides, being effective in reducing the frequency, severity and duration of the

symptoms. The preparations can also be used to treat the acute attacks of the above arthritides reducing their duration, severity and associated symptoms.

It is also believed that the efficacy of the compositions of the present invention can be enhanced by the presence of gamma linoleic acid. Thus, the compositions may comprise, in addition to a sesquiterpene lactone and a B-complex vitamin, gamma linoleic acid or a source thereof. The linoleic acid source may be, for example, evening primrose oil or borage oil.

For the treatment of asthma, preparations in accordance with the invention may be administered orally, or parenterally and conveniently take the form of a tablet, capsule, injectable, liquid suspension or elixir. Circumstances may arise where it is best administered by suppository, inhalation, slow release implant, slow release patch or other topical vehicle. Dosage and administration are as indicated above.

A preparation in accordance with the invention may be co-administered with or additionally include other ingredients such as bronchodilator, antihistamine and anti-infective agents, examples of which agents are:

isoprenaline sulphate,
orciprenaline,
adrenaline,
terbutaline sulphate,
theophylline,
brazilian cocoa
choline theophyllinate,
aminophylline,
ephedrine hydrochloride,
papaverine hydrochloride,
ipratropium bromide,
atropine methonitrate,
beclomethasone dipropionate,
fenoterol hydrobromide,

betamethasone,
isoetharine mesylate or hydrochloride,
phenylephrine hydrochloride or bitartrate,
thenyldiamine hydrochloride,
reproterol hydrochloride,
deptropine citrate,
butethamate citrate,
acepifylline,
diphenylpyraline hydrochloride,
sodium cromoglycate,
etamiphylline camsylate,
theophylline monoethanolamine,
etafedrine hydrochloride,
bufylline,
guaiphencain,
diphenydramine hydrochloride and other histamine,
H1-receptor antagonists,
diprophylline,
methoxyphenamine hydrochloride,
rimiterol hydrobromide,
hyoscine hydrobromide,
salbutamol sulphate,
ketotifen hydrogen fumarate,
pseudo-ephedrine hydrochloride,
bromhexine hydrochloride, and
antifungal, antibacterial and antiviral agents.

The composition in accordance with the present invention is believed to be useful in the treatment of bronchial asthma, bronchoconstriction associated with chronic bronchitis, and symptoms associated with histamine release in allergic hypersensitivity phenomena such as hay fever and anaphylaxis.

Compositions in accordance with the invention will now be illustrated in more detail with reference to the following Examples:

EXAMPLE 1

Preparation of Capsules:

Powdered feverfew leaf and riboflavin are mixed in the following proportions:

standardized feverfew leaf powder (containing at least 0.2% parthenolide)	125 mg
riboflavin	400 mg

The mixture is encapsulated into a soft shell capsule or hard shell capsule or two piece hard shell gelatin capsules. The capsules may be treated to retard disintegration or absorption by the use of gastro-resistant coatings, such as hydroxymethyl propyl cellulose, or the content may be mixed with polymeric matrix materials as those known to the pharmaceutical industry, to release the active ingredients at a controlled rate. The soft shell or two piece hard shell gelatin capsule may be used via the oral or rectal route.

EXAMPLE 2

Preparation of tablets:

The following ingredients are mixed in the given relative proportions:

standardized feverfew leaf powder (rich in sesquiterpene lactones)	60 mg
riboflavin	200 mg
milk sugar (powder)	150 mg
starch	44 mg
talc	40 mg
stearic acid	1.4 mg
tartaric acid	as required

All ingredients are mixed thoroughly. Sufficient tartaric acid should be used in this mixture to adjust the pH to between 2 and 6.5, preferably to pH 4.5. The mixture is compressed into slugs, which are ground and screened to 14-16 mesh granules, which are then recompressed into tablets.

The tablets may be enteric coated, sugar coated, film coated or prepared as a laminated tablet. Two tablets are recommended for daily ingestion.

EXAMPLE 3

Preparation of injectable:

The following are mixed:

parthenolide	2500 μg
riboflavin	2 g
USP water for injection	10 ml

The pH is adjusted to between 2 and 6.5, using HCl.

The injectable may be administered by intramuscular, subcutaneous, or intravenous injection. The preparation should be stored in tight, light-resistant containers, preferably between 15-25° C.

EXAMPLE 4

Preparation of caplets:

The following ingredients are mixed in the given relative proportions:

standardized feverfew leaf powder (rich in sesquiterpene lactones)	60 g
riboflavin	750 g
starch	95 g
lactose	42 g
zein	45 g
magnesium stearate	8 g

The mixture of riboflavin, starch and lactose is granulated with zein (10% in ethyl alcohol, adding additional alcohol if necessary to obtain good wet granules). The granulated mixture is wet screened through 8 stainless steel screen and dry at 40 to 50°C, and is then dry screened through a #20 stainless steel screen. Feverfew leaf powder is then added, which has been screened using a #8 stainless steel screen. The composition is then mixed thoroughly, lubricated and compressed into caplets. Each caplet should weigh 500 mg.

Caplets may be enteric coated, sugar coated, film coated or prepared as a laminated tablet.

EXAMPLE 5

Preparation of suspension:

The following are mixed:

methyl cellulose	0.5 g
standardized feverfew leaf powder (rich in sesquiterpene lactones)	2.0 g
riboflavin	4.0 g
purified water	100 ml
benzoic acid (preservative)	0.1 g
flavoring agent (e.g.: vanillin)	0.1 ml

The dry solids are triturated and the purified water is slowly added with trituration. The pH is adjusted to between 3 and 6.5 using HCl as required.

The suspension may be administered by ingestion. The preparation should be stored in tight, light-resistant containers, preferably between 15-25°C.

What is claimed is:

1. A pharmaceutical composition useful for alleviating migraine and related headaches, arthritis and asthma comprising:

A) a sesquiterpene lactone; and

B) a B-complex vitamin.

2. The composition of claim 1 wherein the sesquiterpene lactone is provided by a source selected from the group consisting of plant materials and plant extracts containing sesquiterpene lactone.

3. The composition of claim 1 wherein the sesquiterpene lactone is provided by a source selected from the group consisting of feverfew leaf powder and feverfew extract.

4. The composition of claim 1 wherein the sesquiterpene lactone is provided by a source selected from the group consisting of *Asteracea* leaf powder and *Asteracea* extract.

5. The composition of claim 1 wherein the sesquiterpene lactone is provided by a source selected from the group consisting of *Magnoliacea* leaf powder and *Magnoliacea* extract.

6. The composition of claim 1 wherein the sesquiterpene lactone is parthenolide.

7. The composition of claim 1 wherein B-complex vitamin is riboflavin.

8. The composition of claim 3 wherein the B-complex vitamin is riboflavin.

9. The pharmaceutical preparation of claim 1 which comprises feverfew leaf powder in combination with riboflavin.

10. The pharmaceutical preparation of claim 1 which comprises parthenolide in combination with riboflavin.

11. The pharmaceutical composition of claim 1 in the form of a tablet, capsule, caplet, lozenge, suspension, elixir, injectable, inhalant, suppository, slow-release implant, slow-release patch or other topical vehicle.

12. The pharmaceutical composition of claim 3 in the form of a tablet, capsule, caplet, lozenge, suspension, elixir, injectable, inhalant, suppository, slow-release implant, slow-release patch or other topical vehicle.

13. A method of treating a patient suffering from an illness selected from the group consisting of migraine, arthritis, and asthma by administering to said patient both a source of sesquiterpene lactone and a B-complex vitamin, in a therapeutically effective amount.

14. The method of claim 12 wherein the sesquiterpene lactone and the B-complex vitamin are administered by independent dosage forms.

15. The method of claim 12 wherein the sesquiterpene lactone and the B-complex vitamin are administered in the same dosage form.

16. A method of preventing or reducing the severity of an illness selected from the group consisting of migraine, arthritis, and asthma by administering to said patient both a source of sesquiterpene lactone and a B-complex vitamin, in a prophylactically effective amount.

17. The method of claim 15 wherein the sesquiterpene lactone and the B-complex vitamin are administered by independent dosage forms.

18. The method of claim 16 wherein the sesquiterpene lactone and the B-complex vitamin are administered in the same dosage form.

19. The composition of claim 1 also comprising gamma linoleic acid.

20. The composition of claim 19 wherein gamma lineoleic acid source is selected from the group consisting of evening primrose or borage oil.

21. The composition of claim 20 wherein the source of sesquiterpene lactone is feverfew and the B-complex vitamin is riboflavin.

22. The composition of claim 1 comprising feverfew, riboflavin, and a nonsteroidal anti-inflammatory drug.

23. The composition of claim 22 wherein the nonsteroidal anti-inflammatory drug is of plant origin.

24. The composition of claim 23 wherein the nonsteroidal anti-inflammatory drug is white willow bark or its extracts.